American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

JOSEPH ROSIN
Remington Medalist
1945

Since 1825 *October 1945*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43rd Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $3.00 **Foreign Postage, 25 Cents Extra**
Single Numbers, 30 Cents **Back Numbers, 50 Cents**

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

Oh, Boy! just two more weeks

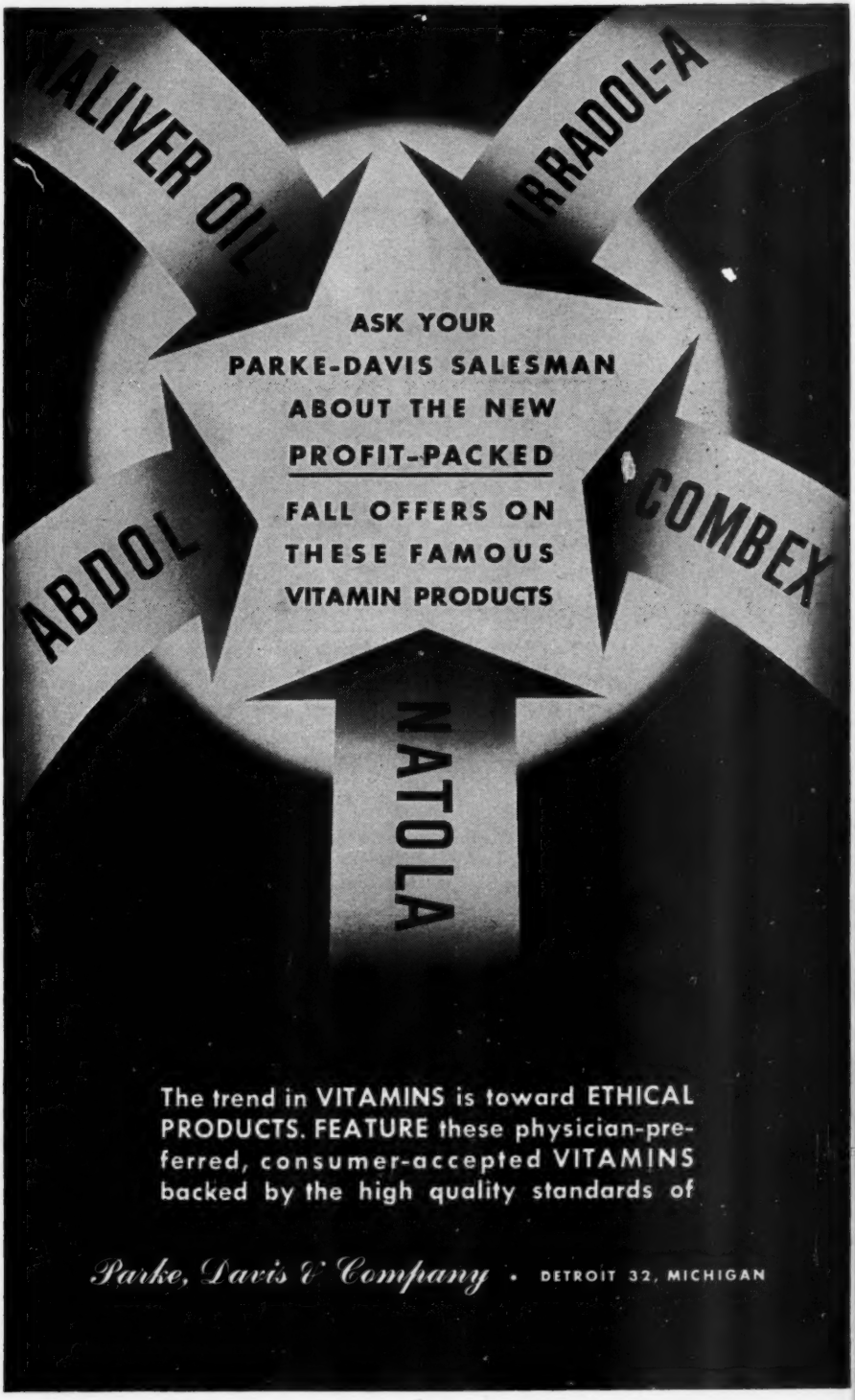
Things had looked pretty good for the Northside Hornets until young Bill Wilkins broke his leg in the first scrimmage of the season. Bill was tough, but not so tough that his tibia didn't snap when twisted under the weight of three enthusiastic tacklers. Then followed days of hospitalization, with the inevitable cast and long hours of patient waiting. Now everything was to be all right, for only this morning Dr. Perry had said, "Just two more weeks, Bill, and you'll be as good as new." Bill knew that when Dr. Perry said "two weeks," he meant just that. All his life he had been taught to respect Dr. Perry and to rely on his judgment. It never occurred to him to question the doctor's decision.

Through the years, Eli Lilly and Company has sought to deserve for itself and for Lilly Products the confidence and respect of the physicians and pharmacists whom it serves. There have been no secrets, no duplicity, no subterfuge. The full and complete formula of every Lilly Product is always available. Quality is the first consideration in manufacturing procedures. From the selection of the crude materials to the testing of the finished product, there is no compromise. Every single Lilly Product must be worthy of the name it bears.

Physicians and pharmacists everywhere can have the same confidence in Lilly Products that young Bill Wilkins has in Doctor Perry.

WE PAY HIM · BUT HE WORKS FOR YOU ·

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.


ALIVER OIL
IRRADOL-A
ASK YOUR
PARKE-DAVIS SALESMAN
ABOUT THE NEW
PROFIT-PACKED
FALL OFFERS ON
THESE FAMOUS
VITAMIN PRODUCTS
ABDOL
COMBEX
NATOLA
The trend in VITAMINS is toward ETHICAL PRODUCTS. FEATURE these physician-preferred, consumer-accepted VITAMINS backed by the high quality standards of
Parke, Davis & Company • DETROIT 32, MICHIGAN

88%

of patients with rheumatoid arthritis may expect marked diminution or complete relief of all subjective and objective symptoms when treated with

SOLGANAL-B OLEOSUM

is highly efficient, produces lasting benefits in most cases and exhibits minimal toxicity.

SOLGANAL-B OLEOSUM (aurothioglucose), a water-soluble gold compound suspended in oil for gradual and prolonged absorption, is available in ampules and vials for intramuscular injection.

TRADE-MARK SOLGANAL-B OLEOSUM
REG. U. S. PAT. OFF.

SCHERING

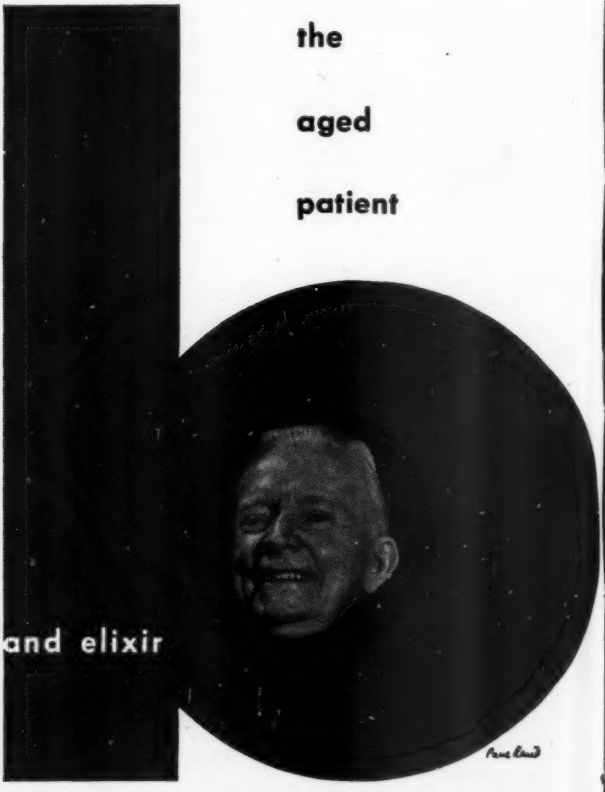
Schering CORPORATION • BLOOMFIELD, N. J.

when persistent depression settles upon

the

aged

patient



benzedrine sulfate
(racemic amphetamine sulfate, S. K. F.)

tablets and elixir

Old age sometimes brings a severe and lasting depression, marked by self-absorption, withdrawal from former interests and loss of capacity for pleasure. This characteristic depression often aggravates underlying pathology by interfering with exercise, appetite and sleep.

Because of its power to restore mental alertness and zest for living, Benzedrine Sulfate is of special value in the management of depression and anhedonia in the aged. Obviously, careful observation of the aged patient is desirable; and the physician will distinguish between the casual case of low spirits and a true and prolonged mental depression. The dosage should be adjusted to the individual case.

Smith, Kline & French Laboratories, Phila., Pa.

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 117. OCTOBER, 1945 No. 10

CONTENTS

OUR COVER

JOSEPH ROSIN

Remington Medalist For 1945

THE selection of Joseph Rosin as the recipient of the Remington Medal gives recognition to one of the most worthy individuals serving American Pharmacy for over three decades.

For those familiar with the complex questions arising in the formulation and revision of chemical texts in the U. S. P. and N. F. the contributions of Joseph Rosin are known to be of primary importance. This fact was recognized by the Committee on Award in naming the medalist this year when they cited him as "the foremost American authority on chemical reagents" and stated that the Pharmacopœia and National Formulary "are today more indebted to Mr. Rosin for the excellent quality of their chemical standards than to any other person."

The medalist is also well known as the author of the book "Reagent Chemicals and Standards" and as one of the principal authors of the "Merck Index." The pharmaceutical and chemical literature has received many scientific papers by this author and his assistants. He is at present a vice-president of Merck and Company, Inc., Rahway, N. J., and one of the firm's directors. Many scientific societies list and recognize Joseph Rosin as one of their distinguished members: the American Pharmaceutical Association, the American Chemical Society, the American Institute of Chemists, the American Institute of Chemical Engineers, the London Chemical Society, the Society of Sigma Xi.

To those who know Joseph Rosin well this honor of receiving the Remington Medal brings genuine happiness, for he is a living example of the true scientist, scholar and friend—thorough, painstaking and diligent yet quiet, reserved and modest in the evaluation of his own achievements.

EDITORIAL

IS PHARMACY A TRADE OR A PROFESSION?

A RECENT announcement from the United States Civil Service Commission asks the cooperation of all editors of pharmaceutical publications in recruiting pharmacists for service in government hospitals. No one can question the need of competent pharmacists in such work but it is questionable whether competent personnel will be placed in these positions when one examines the necessary qualifications for these positions.

A candidate is considered eligible if he or she has had *practical experience* totaling three years in a pharmacy in lieu of a formal education in a college of pharmacy. In the same paragraph the candidate is required to have "(a) a knowledge of the fundamental principles of pharmacy, chemistry, therapeutics, pharmacology and related subjects and (b) a working knowledge of these subjects."

It is evident to one who is familiar with pharmacy and pharmaceutical education that the person responsible for these requirements is an ass when it comes to a knowledge of pharmacy since otherwise such contradictory and completely irreconcilable prerequisites could not possibly have been drawn up.

No person could possibly have a sound knowledge of the sciences underlying pharmacy in these modern times without a formal education in the field, any more than could a person be qualified in medicine without graduation from a college of medicine. Neither are the examinations that are proposed as a final check on the qualifications conclusive in their results.

If it were the policy of the Civil Service Commission never to require college training as a fixed prerequisite for any government position, the situation with respect to pharmacists might not be so deplorable, but surely a pharmacist is in greater need of college training than a dietitian or a physical training instructor and yet these candidates must be college trained!

Government services should set an example of efficiency and quality in public institutions and not be content with the minimum

standard to be found in private enterprise. Of our forty-eight states, forty-five now require graduation from a recognized college of pharmacy as a prerequisite to the practice of pharmacy and the state examinations for the license to do so. Should then persons of poorer qualifications be permitted to render pharmaceutical service in government hospitals? We think there is but one honest answer. Of course not.

The efforts of the American Pharmaceutical Association, through its Secretary, to remedy this situation, deserve the support of all pharmaceutical groups and pharmacists individually. Our representatives in Washington should know the facts of this matter and be made to realize that public welfare here is at stake. Our efforts to contact Senators and members of the House are not to be construed as those of another pressure group. Not by any means. It is only that we, who can appreciate the type of service to be required of pharmacists in the government employ, feel that public interest demands only properly trained personnel. To remain silent places upon us the responsibility for permitting a type of pharmaceutical service in government hospitals and elsewhere that may result in serious consequences.

L. F. Tice.

Correction

Classification and Hardness of Granulations. In this article in the August, 1945, issue of this Journal the abscissas should read "minutes" and the ordinates should read "per cent reduction of forty mesh."

QUANTITATIVE DETERMINATION OF DEMEROL AND ITS SEPARATION FROM OPIUM ALKALOIDS

By Charles Milos *

THE free base or ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid can be completely removed from an alkaline salt solution by distillation. By titrating the distillate with an acid of known normality the amount of demerol present can be ascertained. This method of isolating the free base separates the demerol from opium alkaloids and their common adulterants.

At ordinary room temperature the free base is a liquid. When heated on a steam bath it is slowly volatilized.

Method

Dissolve a known weight of sample in 10 ml. of water. If the sample does not dissolve readily, add a few drops of glacial acetic acid and warm on a steam bath. Transfer to a 500 ml. Erlenmeyer flask. Wash the dish twice with a few ml. of water. To the combined aqueous solution add 80 ml. of saturated sodium chloride solution. Drop a small piece of acid litmus paper into the flask, then add powdered calcium hydroxide, stirring the solution by rotating the flask until the solution is definitely alkaline. Add a few pieces of pumice and attach the flask to a thoroughly cleaned condenser, equipped with a Kjeldahl bulb. Distill over 60 ml. Allow the flask to cool, add 5 ml. of 95% U. S. P. ethyl alcohol and heat until all of the alcohol has been distilled. Remove the flask and Kjeldahl bulb and flush the condenser with a little water. To the distillate add two drops of methyl red indicator and titrate with N/100 sulphuric acid. Each ml. of N/100 acid is equivalent to 0.002836 gram of demerol. Sulfuric acid N/10 may be used if a burette graduated to 0.05 ml. is available.

Transfer the distillate to a separator, add two drops of concentrated hydrochloric acid, and extract with chloroform. Use 10 ml. portions and repeat until the methyl red is completely removed. Dis-

* Contribution from the New York Field Laboratory of the Alcohol Tax Unit, Bureau of Internal Revenue.

card the chloroform. Add ammonium hydroxide (10% solution) until alkaline, and extract with chloroform. Make three extractions, using 10 ml. portions. Combine the chloroform in another separator and wash with 5 ml. of water. Filter the chloroform into a dish, add 5 ml. of isopropyl alcohol and distill off the chloroform over a steam bath.

To the remaining alcoholic solution add 10 ml. of 95% U. S. P. ethyl alcohol saturated with hydrogen chloride. Evaporate to dryness. Dissolve the residue in 10 ml. of c. p. methanol, evaporate to dryness and cool in a desiccator. If the residue is not crystalline, rub it with a clean glass rod and crystallization will take place. Determine the melting point. With known samples of demerol processed in this manner the uncorrected melting point was 184° C. The corrected melting point was 187-188° C.

Demerol when treated with 5 to 6 drops of fuming nitric acid, heated to dryness, cooled, and then treated with a few drops of 2% alcoholic KOH, gives a deep red color. Concentrated nitric acid fails to give this reaction.

D'Allessio de Carnevale Bonino (1) gives a number of color reactions for demerol. These reactions are based on nitration, reduction, diazotization and coupling with phenol.

A series of microchemical tests are described by Levine (2) for demerol with a large number of alkaloidal reagents. Plates illustrating the various types of crystalline precipitates obtained with some of the alkaloidal reagents are shown.

Table I shows the results of experiments conducted with demerol, and demerol adulterated with milk sugar.

TABLE I

	Used:		Found:
No.	Demerol in mg.	Sugar in mg.	Demerol in mg.
1	45		44.5
2	90	1000	88.8
3	93		91.9
4	29.7	1000	27.9
5	175.2	2000	173.8
6	Tablet alleged to contain 50 mg.		48.0

A number of experiments were conducted with mixtures containing demerol, morphine sulphate or heroin hydrochloride of known

percentage, milk sugar and starch. Table II shows the results of these experiments. The maximum amount of sugar or sugar and starch used in any one experiment was 2 grams.

TABLE II

	Added in mg.			Found in mg.		
No.	Demerol	Anhyd. Morphine	Anhyd. Heroin	Demerol	Anhyd. Morphine	Anhyd. Heroin
1	23.6	103.4		22.7	104	
2	83.1		73.5	82.2		72.2
3	39.3		35.1	39.7		33.8
4	100	63.3		99.3	64	

The following procedure was used in isolating and determining the amount of opium alkaloid:

1. Add sufficient water to the residue in the Erlenmeyer flask to dissolve all of the precipitated salt. If heroin was present in the original sample acidify with sulfuric acid to make the solution approximately one normal. Reflux 45 minutes, cool and transfer to a separator. Wash the flask with a few ml. of water. In the absence of heroin acidify with acetic acid and transfer to a separator.

2. After adding sufficient ammonium hydroxide to make the solution alkaline, extract with chloroform containing 15% by volume of isopropyl alcohol. Make 4 extractions, using 20, 10, 10 and 5 ml. portions. Combine the chloroform in a separator and discard the aqueous solution.

3. Scrub the chloroform twice with alkaline salt solution (sat. sodium chloride solution + 2 grams sodium hydroxide per 100 ml.), using 20 and 10 ml. portions. Discard the chloroform and combine the alkaline salt solution in a separator.

4. Extract the alkaline salt solution once with 10 ml. of chloroform. Discard the chloroform.

5. Add glacial acetic acid to the alkaline salt until acidic and 0.5 ml. in excess. Now add ammonium hydroxide 10% solution until alkaline and extract with chloroform containing 15% by volume of isopropyl alcohol. Make 4 extractions, using 20, 10, 10 and 5 ml. portions. Combine the chloroform in a separator.

6. Wash the combined chloroform with 5 ml. of water and filter into a dish. Wash the water with a few ml. of the chloroform-isopropyl alcohol solvent, and filter into the dish.

7. Evaporate to dryness on a steam bath. Dissolve the residue in 5 ml. c. p. methanol and evaporate to dryness. Cool in a desiccator and weigh.

Morphine x 1.295 = Heroin.

Summary

1. A method is given for the quantitative determination of demerol.

2. Demerol can be separated from any substance which cannot be steam distilled from an alkaline salt solution.

3. Heroin is partially converted into morphine. Completing the inversion and isolating the morphine is the most direct method of determining the amount of heroin.

Acknowledgment

For the demerol placed at his disposal the author wishes to express his appreciation to Mr. Geo. W. Romig, Jr., Chemist in Charge of the New York Laboratory.

REFERENCES

1. *C. A.*, *37*:3024 (1943).

2. *Ind. & Eng. Chem.* (Analytical Edition), Vol. 16, No. 6, page 408 (June, 1944).

The amount of energy fixed annually by plants through photosynthesis is estimated at the equivalent of 300,000,000,000 tons of coal. A fact frequently overlooked is that sugar is the starting point in the production of all naturally occurring organic compounds and thus the most important organic substance in the world.

RECENT ADVANCES IN DRUG THERAPY †

By Samuel W. Goldstein *

WE have come a long way from the oils, herbals and mysticism of the medicine man; from the unguents and simple mixtures of Egypt; from the simplified and supposedly complete materia medica of the Arabians; from the unclean and stinking medicines of the dark ages; and from the enlightened era of blood-letting. We have not gone too far beyond Galen and Paracelsus that we cannot see their influence in the pharmaceuticals used today; we have not gone much beyond Pasteur in the bacteriological field; for, in addition to his vaccine and antitoxin contributions, he surmised that there must be something in the soil that inactivated the anthrax bacillus. We have not gone beyond Ehrlich, the originator of chemotherapeutic concepts, the discoverer of a specific for the syphilis-causing bacterium and the seeker for a single substance which would rid the human host of all its undesirable parasitic invaders. But we do not live in a static period. The advances that have been made in recent years toward Ehrlich's goal of the universal purifier are amazing, especially when compared with the progress achieved in the centuries from the alchemists' blind groping for the philosopher's stone, which was to confer eternal youth and health, to the modern chemotherapeutic era.

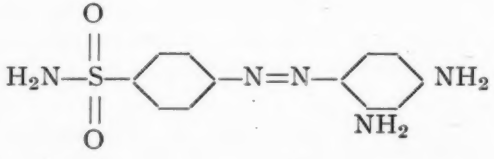
It has been said that human progress takes place in three stages; the adoptive, the adaptive and the creative. Certainly these three stages can generally be applied to the development of therapeutic remedies. It is well known that the South American natives found that by chewing the leaves of the coca plant certain stimulating effects were obtained, and hunger pangs were allayed because, as we now know, the terminals of the gustatory nerves were paralyzed. This was a case of adoption. In 1860, Niemann (1) isolated the alkaloid cocaine, and Koller (2), who in 1884 reported his results with cocaine in ophthalmology, demonstrated its use for the production

† Given before the Maryland Academy of Medicine and Surgery.

* Pharmaceutical Chemist, Bureau of Chemistry of the Maryland State Department of Health.

of local anesthesia, and thereby adapted the drug to new uses. In 1885, Merck (3) and Skraup (4) attained the creative phase by synthesizing the alkaloid in the laboratory; and in 1909 this phase was extended when there were made available purely synthetic local anesthetics, such as novocaine or procaine (5), which have no counterpart among natural products. Today, after going through the first two phases with opium and morphine, and with the suprarenal gland and epinephrine, and with ma huang and ephedrine, we find the synthetic demerol being advocated as a substitute for morphine under certain conditions and for epinephrine and ephedrine in cases of bronchial asthma (6). In addition we have the many synthetic derivatives of epinephrine and ephedrine which are still being studied, as well as other synthetic analgesics.

Now let us look at the sulfa drugs. At first glance one might say, here we have a class of medicinal drugs that skipped the two earlier stages and developed from the creative stage only; since there is no known sulfonamide in nature. But let us go back a bit. In 1908 Gelmo (7), an organic chemist, prepared para-amino-benzene-sulfonamide (now known as sulfanilamide), but not because he was synthesizing a natural or new product having clinical activity. Apparently he wanted only to try out a chemical reaction and then identify the products formed. So man here replaced nature in the first production of a compound. In its adoptive stage it was used only as a means to a non-therapeutic end, for about 1910 Horlein (8) and his associates prepared a number of azo dyes with sulfonamide and substituted sulfonamide groups. They found that dyes containing a sulfonamide group entered into a more intimate combination with the protein cells of wool and possessed a greater degree of fastness to washing than dyes without this group. In 1932 Mietzsch and Klarer (9) synthesized the azo dye, sulfonamido-chrysoidine,



now known as prontosil. In 1935, Domagk (10), after testing many dyes, reported that mice infected with a virulent *Streptococcus*

hemolyticus culture survived if treated with sulfonamido-chrysoidine, but that untreated mice died. Soon widespread clinical use of the drug began. Tréfouël, Tréfouël, Nitti, and Bovet (11) postulated that the azo-sulfonamide compounds split through the azo linkage in the body and that one or more of the cleavage products was responsible for the therapeutic activity. They calculated that sulfanilamide was one of the active cleavage products, and tests with the simpler compound proved them to be correct. Then, years after its first preparation, sulfanilamide was introduced as a therapeutic agent. The completion of the adaptive phase was the signal for the release of a burst of creative energy such as chemotherapy had never experienced. Thousands of derivatives of sulfanilamide have been synthesized and tested for therapeutic activity. The sulfonamides most generally accepted and the organisms against which they appear to be most effective may be listed as follows: Succinylsulfathiazole—gram-negative organisms of the intestine, and *B. dysenteriæ;* Sulfacetamide—urinary tract infections, especially *B. coli;* Sulfadiazine—streptococcus, pneumococcus and meningococcus; Sulfaguanidine—*B. dysenteriæ;* Sulfamerazine—pneumococcus, hemolytic streptococcus and meningococcus; Sulfapyridine—pneumococcus; Sulfathiazole—gonococcus (best sulfa), pneumococcus and staphylococcus.

That the sulfonamides have been and will continue to be a powerful weapon against our disease-producing enemies there is no doubt; nor is there any doubt that as the knowledge of their activity and undesirable side actions increases, the necessity for their careful prescription and supervised administration becomes more imperative.

Another similar story can be recited about the synthesis, neglect, rediscovery and present uses of the compound 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane (dichloro-diphenyl-trichloroethane) or DDT. Since in a strict sense this is an insecticide rather than a therapeutic drug I will limit myself to a quotation by General J. S. Simmons (12) of the Surgeon General's Office. He said, "I feel quite sure that the knowledge gained of this amazing chemical constitutes the most valuable single contribution of our wartime medical research to the future health and welfare, not only of this nation but of the world." His statement can be readily appreciated when the world-wide prevalence of malaria is considered. However, new

problems will confront us. For instance, how will a country like India keep the malaria survivors from starving?

The parts played by the individual amino acids in protein nutrition are gradually being clarified. Symptoms attributable to deficiencies of different amino acids have been defined, and the present tendency is to consider the amino acids loosely along with hormone and vitamin functions. There is no doubt that under certain conditions, such as gastro-intestinal diseases or where digestion and assimilation are impaired, there may be a deficiency of amino acids because the normal amounts cannot be consumed and bacterial synthesis in the intestines is interrupted. These conditions will be recognized more as the field of geriatrics, involving studies of the diseases of old age, is developed. In these cases parenteral administration of preparations containing the simple amino acids are of value. Predigested protein preparations have been prepared for oral administration and their uses are being studied. The average American diet appears to contain a sufficient amount of amino acids, but if you feel that you would like to increase your intake you might try an extra cheese sandwich.

Sizer and Prokesch (13) discovered that mushroom tyrosinase, besides being an oxidase of the amino acid tyrosine, can render the poison of poison ivy harmless. All previously reported oxidases with this property have been found in the poisonous Rhus sap along with the poison itself. They hold out the hope that this mild enzyme may replace the stronger oxidants now used in the treatment of poison ivy dermatitis.

An instance in which man uncovered an enemy and through chemotherapy converted it to a friendly agent, can be seen in the story of dicoumarol, 3-3′-methylene-bis(4-hydroxycoumarin). A type of hay intoxication long noted in cattle raised in the Middle West was studied about twenty years ago by Schofield (14) and Roderick (15). The effects were noted when spoiled sweet clover (*Melilotus alba* or *M. officinalis*) was present and the condition was called "sweet clover disease." This is characterized by an almost complete loss of the clotting power of the blood. It was shown that the reduced clotting power of the blood is due to destruction or inactivation of prothrombin (16, 17). After a period of fruitless attempts the toxic agent, dicoumarol, was extracted (18, 19) from spoiled sweet clover, and, after chemical analysis, the substance was synthesized by Stah-

mann (20) and his colleagues. Tests on animals indicated that a nontoxic controlled fall in the prothrombin index is obtainable with dicoumarol. Lehmann (21) found that oral doses of 0.25 to 1.0 Gm. of dicoumarol produce in man a fall in the prothrombin index similar to that produced in lower animals, usually without toxic effects. Seventeen cases of thrombosis were treated with clinical improvement in all cases. Oral administration of the drug for the prevention of postoperative thrombosis is now under investigation. Recently Goth (22) published a report showing that dicoumarol has marked antibacterial properties. It is not inconceivable that we might soon hear of dicoumarol or a substance with a similar activity being used along with penicillin to counteract the latter's tendency to shorten the blood clotting period and at the same time to enhance its antibacterial activity. In fact heparin, an anticoagulant, is already being used to prevent fibrin deposition along with penicillin therapy in subacute bacterial endocarditis (23, 24).

Curare is not a new drug. It was used as an arrow poison by the Amazon witch doctors, and was supposedly carried to Europe by Sir Walter Raleigh. We recall it from our studies only as something which other drugs had an action like: a curare-like action. The latest use of this phrase is the reference to the curare-like action of the erythrina alkaloids which are being used for the relief of various spastic conditions due to nervous disorders, and to control the violence of convulsions due to metrazol in the shock therapy of certain mental diseases (25). Now Griffith (26) reports that the introduction of curare into medicine has made it possible for surgeons to obtain complete abdominal relaxation at any time during anesthesia produced with nontoxic, controllable anesthetic agents, especially cyclopropane. However, it is advisable that no curare be used without having present and in readiness for administration a prostigmine preparation which is an effective antidote for curare.

Thiouracil, a derivative of thiourea, has shown good results in the treatment of thyrotoxicosis causing hyperthyroidism. The drug causes a drop in the basal metabolic rate and at least postpones the necessity of surgical treatment. However, Fishberg and Vorzimer (27) report that definite and sudden granulopenia (reduction of white blood cells) was observed in 20 per cent of their patients treated with thiouracil. They suggest that a white blood count be made every second or third day, and that the patient should be given

only enough of the drug to last until the next blood count. Pyridoxine, vitamin B_6, in prophylactic doses of 150 mg. daily by mouth, at present seems to be the best method of protecting the bone marrow functions during thiouracil medication. Sulfonamides because of their tendency to induce agranulocytosis are contraindicated during thiouracil therapy.

When the antibacterial use of a substance obtained from a mold was announced there were many who could say, I remember when the old folks placed moldy bread on sores as a healing agent. No one will ever know how many bacteriologists sadly discarded mold-contaminated agar culture plates before Fleming (28) noted that "sterile" zones had formed around the mold colonies which had contaminated his staphylococci-inoculated plates. Fleming discovered that an antibacterial substance was produced by the mold, which happened to be a strain of *Penicillium,* and he named the substance penicillin. .Bacteriological tests were made with broth in which the mold had grown, and while these tests showed that the substance was active against the pyogenic cocci, certain gram-positive bacilli, and ineffective against the colon-typhoid group and many other gram-negative organisms, the work was stopped at this stage. It was not much further advanced in 1936 when Florey and his associates at Oxford started a systematic study of the chemical and biological properties of antibacterial substances produced by micro-organisms. By good fortune, one of the first such substances to be investigated was penicillin, and the report (29) published in 1940 marked penicillin as a definite substance with clinical possibilities.

In the meantime another worker, Dubos (30), in 1939, had become the first to isolate in clinically usable form an antibacterial agent from a micro-organism. He isolated tyrothricin from peptone cultures of the soil organism *Bacillus brevis.* Tyrothricin, which was later found to be composed of the two substances, gramicidin (15-20 per cent) and tyrocidine (80-85 per cent), was too toxic upon injection and had no action when taken orally. Its field of usefulness is limited to topical application such as irrigation of infected areas.

In 1941, the Oxford group reported the first clinical use of penicillin (31). There then followed a period of intense study by cooperating groups of research workers, including the drug manu-

facturers, to find the best conditions for the mass production of this new "magic bullet." That these efforts were crowned with amazing success is well known, and the part played by those professional pharmacists, the drug manufacturers, has been duly recognized.

Three chemically different penicillins, F, G and X, have been isolated. Penicillin G predominates in commercial preparations, although 20 to 25 per cent of penicillin X may be present. Penicillin F has been produced to some extent in Great Britain, but it is thought to be less stable and not quite as potent an antibiotic as penicillins G and X. Penicillin X appears to be the most potent against pneumococci, and is also most effective in the treatment of gonorrhea (32). Most of the penicillin is now being prepared in the form of the sodium or calcium salt, because these salts are more stable than the free acidic substance. Cavallito (33) and his associates have reported that the benzyl ester of penicillin is much more effective than penicillin sodium. Here is a partial summary of the clinical uses of penicillin from a report by Keefer (34) and his associates on the new dosage forms of penicillin for intravenous, intramuscular and oral administration. This drug has been found to be the best therapeutic agent available for the treatment of all staphylococcic infections with and without bacteremia; all cases of clostridia infections (gas gangrene, malignant edema); all hemolytic streptococcic infections with bacteremia and all serious local infections; all anaerobic streptococcic infections; all pneumococcic infections of the meninges, pleura and endocardium, and all cases of sulfonamide-resistant pneumococcic pneumonia; all gonococcic infections; all cases of anthrax; all cases of chronic pulmonary suppuration in which surgical treatment is contemplated; all meningococcic infections failing to respond to sulfonamides; and all cases of bacterial endocarditis due to susceptible organisms. Penicillin also has been found to be an effective agent in syphilis, actinomycosis, and diphtheria, especially in horse serum-sensitive patients, but these latter uses are not definitely established. When the many conditions that yield to penicillin therapy are noted it seems that Ehrlich's dream of a universal purifier may some day come true.

While the first reports indicated that this drug showed no appreciable undesired reactions, further study has shown that some ill effects may occur. Moldavsky (35) and his associates reported that as the concentration of penicillin in the blood increases, the clotting

time falls. This is associated with the tendency toward thrombosis noted when penicillin is administered intravenously.

A great amount of pharmaceutical research has been and is being carried out to find ideal preparations for the oral and topical administration of this truly remarkable remedy; and some firms have already announced that ointments, nose drops, eye drops, tablets and chewing gum containing penicillin are ready for the public. A most delicious form of medication was produced by mixing penicillin with ice cream. The product was effective in the treatment of streptococcus throat infections, scarlet fever, trench mouth, gingivitis, stomatitis and tonsillitis. Imagine little children smiling happily when mother mentions the doctor. They will remember him as that nice man who lets them stick out their tongues and then tells mother to buy them some ice cream.

Other antibiotic substances have been isolated and studied. Waksman (36), in 1943, classified the known antibiotics into seven distinct chemical groups, and divided them on the basis of toxicity into relatively nontoxic compounds, such as penicillin, citrinin, pyocyanase and actinomycetin; fairly toxic antibiotics like gramicidin, tyrocidine, streptothricin and gliotoxin; and highly toxic actinomycin. Streptothricin, derived from *Streptomyces lavendulae,* was isolated by Waksman and Woodruff (37) in 1942. This substance not only inhibits the growth of *Escherichia coli* and other gram-negative bacteria not affected by penicillin but also is active against some gram-positive bacteria. In 1944 Schatz, Bugie and Waksman (38) reported the isolation of streptomycin from *Actinomyces griseus.* This proved to be somewhat more active against certain pathogenic gram-negative bacilli, including *Eberthella typhosa,* and to be less toxic for the host. A recent report (39) on the use of streptomycin in the treatment of typhoid concludes that "the presence of streptomycin in the blood, urine and feces in amounts more than enough to kill typhoid bacilli in the test tube, and the clinical improvement during therapy of three patients selected because of the severity of their attacks, strongly suggest that the substance contributed to their recovery, if it did not actually cause it." Thus we see that the development of the antibiotics still proceeds apace.

Blood has for some time been considered the vehicle by which many therapeutic agents are carried to the various parts of the body. We have known that blood as such is a therapeutic agent as is also

blood plasma in cases of shock and blood loss. We have believed that the leukocytes of the blood aided in repelling bacterial invasions. But the work of Cohn (40) and others on the protein constituents of blood and their therapeutic values has greatly enlarged our field of thought on this bloody subject. Cohn states that "the control of infectious diseases by passive immunization with gamma-globulins may well be the largest need of a civilian population for a blood derivative and one to which a civilian population can be expected to contribute in the interests of the modification and control of a children's disease, such as measles, until such time as the immunity of each growing generation is achieved.

"In the fractionation of blood to obtain the gamma-globulins, the red cells and the proteins which they contain, as well as the other plasma proteins, become available for the therapeutic uses for which they are needed; the albumin for the treatment of shock, hypoproteinemia, edema and—prepared in the salt-poor condition—as a diuretic agent; fibrin foam and thrombin as a hemostatic agent; fibrin film as a substitute for a natural body membrane; and the large number of other cellular, protein and lipid components, whose physiological function and chemical nature are only beginning to be explored, for whatever therapeutic purposes may prove the most important."

We must be wary of claims for new remedies until they have been scientifically substantiated. Sometimes people are moved to enthusiastic heights by public reports that a cure for a certain disease has been discovered, and then are terribly let down when, upon investigation, they find the report misleading. Such a case was that of diasone which was trumpeted as a cure for tuberculosis on the basis of a report on its effect upon mice, but which did not show the expected results upon clinical trial. Nevertheless, although only several of the newer remedies have been discussed here, one can see that great things have been accomplished in the past few years, and that with scientists again concentrating upon the prolongation of human life and waging war only against the enemies of all mankind greater achievements should be expected. Who knows, but that some day we may learn how to cure a head cold.

REFERENCES

1. Niemann, A.: *Arch. Pharm., 103,* 129-55, 291-308 (1860).
2. Sollmann, T.: "Manual of Pharmacology," ed. 6, W. B. Saunders Co., Phila., 1942, p. 308.
3. Merck, W.: *Ber., 18,* 2264 (1885).
4. Skraup, Z. H.: *Monatsch. Chem., 6,* 556 (1885).
5. Einhorn, A., and Uhlfelder, E.: *Ann., 371,* 131 (1909).
6. *Clinical Excerpts, 19,* No. 5, 148 (1945).
7. Gelmo, P.: *J. prakt. Chem.,* [2] *77,* 369 (1908).
8. Jenkins, G. L., and Hartung, W. H.: "Chemistry of Organic Medicinal Products," ed. 2, 1943, p. 315.
9. Mietzsch, F., and Klarer, J.: *J. A. M. A., 108,* 48 (1937).
10. Domagk, G.: *Deutsch Med. Wochenschr., 61,* 250 (1935).
11. Tréfouël, J., Tréfouël, Mme. J., Nitti, F., and Bovet, D.: *Comp. Rend. Soc. Biol., 120,* 756 (1935).
12. *Baltimore Health News, 22,* No. 5, 133 (1945).
13. Sizer, I. W., and Prokesch, C. E.: *Sci., 101,* 517 (1945).
14. Schofield, F. S.: *Canad. Vet. Rec., 3,* 74 (1922).
15. Roderick, L. M.: *J. Am. Vet. M. A., 74,* 314 (1929).
16. Roderick, L. M.: *Am. J. Physiol., 96,* 413 (Feb., 1931).
17. Quick, A. J.: *Am. J. Physiol., 118,* 260 (Feb., 1937).
18. Roberts, W. L.: *Summaries of Doctorate Dissertations, Madison, Wis., 190,* 501 (1935).
19. Campbell, H. A., and Link, K. P.: *J. Biol. Chem., 138,* 21 (Mar., 1941).
20. Stahmann, M. A., Huebner, C. F., and Link, K. P.: *J. Biol. Chem., 138,* 513 (Apr., 1941).
21. Lehmann, J.: *Sci., 96,* 345 (1942).
22. Goth, A.: *Sci., 101,* 383 (1945).
23. Katz, L. N., and Elek, S. R.: *J. A. M. A., 124,* 149 (1944).
24. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M.: *J. A. M. A., 124,* 144 (1944).
25. Addinall, C. R.: *Merck Rept., 51,* No. 3, 4-8 (1942).
26. Griffith, H. R.: *J. A. M. A., 127,* 642-44 (1945).
27. Fishberg, E. A., and Vorzimer, J.: *J. A. M. A., 128,* 915-21 (1945).
28. Fleming, A.: *Brit. J. Exptl. Path., 10,* 226 (1929).
29. Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J., and Sanders, A. G.: *Lancet, 2,* 226 (1940).
30. Dubos, R. J.: *Proc. Soc. Exptl. Biol. Med., 40,* 311 (1939).
31. Abraham, E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., and Florey, H. W.: *Lancet, 2,* 177 (1941).
32. Welch, H., Price, C. W., Chandler, V. L., and Hunter, A. C.: *J. A. Ph. A., 33,* 114 (1945).
33. Cavallito, C. J., *et al.*: *Sci., 102,* 150-51 (1945).
34. Keefer, C. S., Herwick, R. P., Van Winkle, W., and Putnam, L. E.: *J. A. M. A., 128,* 1161-64 (1945).
35. Moldavsky, L. F., Hasselbrock, W. B., and Goodwin, D.: *Sci., 102,* 38-40 (1945).
36. Waksman, S. A.: *J. Bact., 45,* 64 (1943).
37. Waksman, S. A., and Woodruff, H. B.: *Proc. Soc. Exptl. Biol. Med., 49,* 207 (1942).
38. Schatz, A., Bugie, E., and Waksman, S. A.: *Proc. Soc. Exptl. Biol. Med., 55,* 66 (1944).
39. Reimann, H. A., Elias, W. F., and Price, A. H.: *J. A. M. A., 128,* 175 (1945).
40. Cohn, E. J.: *Sci., 101,* 51 (1945).

REGARDING THE PROCESSING OF CALCIUM CHLORIDE FROM THE TECHNICAL PRODUCT

By G. J. Kogan *

(Translated From the Russian Magazine "Pharmatsia," Vol. No. 3, pp. 31-32, 1944, by Edgard Yan Allen, M. Sc.)

MANY galenical laboratories produce, for the requirements of their territory, calcium chloride in the form of a 50 per cent solution because its production requires considerably less work than is required to manufacture the crystalline material. Besides that, in a great number of instances in pharmaceutical practice, it is sufficient to use the 50 per cent solution.

The 50 per cent solution is usually obtained either by processing marble chips or chalk with the aid of hydrochloric acid and chlorinated lime, or from technical calcium chloride. The first method is comparatively well known as it is the one which is used more frequently. The second method is employed in the Soviet scale of production from raw material of a determined standard. Technical calcium chloride appears as the by-product of non-pharmaceutical manufacture and frequently contains an admixture of calcium hypochlorite and calcium chlorate. Such raw material is usually not employed because the manufacturing procedure is only determined for the removal of sulfates and metals of the third group. The lack of suitable raw material caused me to make use of the technical product containing an admixture of hypochlorite and chlorate.

To a 25 per cent solution of technical calcium chloride is added hydrochloric acid having a specific gravity of 1.19 estimated at four grams for each kilogram of crystalline $CaCl_2$, and finely cut chips of metallic iron estimated at ten grams for each kilogram of crystalline $CaCl_2$. This mixture is heated until the chlorine is eliminated and the reaction, which must be acid during the entire heating period, must be closely watched (otherwise HCl should be added to maintain acidity). The end of the reaction, i. e., the complete elimination of chlorine, is controlled by moist starch iodide paper (not inserted into the fluid—only into the vapors). After the elimination of chlorine

* The Pharmaceutical Chemical Factory at Tashkend (U. S. S. R.).

the iron is next removed as follows: A little chlorinated lime is added to the acid solution; this mixture is periodically stirred for a period of one-quarter to one-half hour, then the calcium oxide is made alkaline in reaction to phenolphthalein, heated and filtered. The filtrate is neutralized with hydrochloric acid and, judging by the specific gravity, is adjusted to contain 50 per cent $CaCl_2$. $6H_2O$ (evaporation, or oppositely—dilution with water). It is necessary to point out that neither the Pharmacopœia (Φ VII) nor the papers on the "Endeavors" (of the Russian Pharmacopœial Committee) contain any tests for hydrochlorate or hypochlorite contents, but the raw material can contain such added ingredients. The presence of the indicated admixture is usually observed during the heating of calcium chloride with diluted hydrochloric acid through the insertion of moist starch iodide paper into the produced vapors.

Translator's Notice

Since this article deals with the processing of calcium chloride from the technical product, I am including a translation of the "Crystalline Calcium Chloride" monograph from the current Russian Pharmacopœia (Φ VII). This will enable the reader to see what standards must be complied with in order to make this chemical of pharmacopœial quality.

Calcium Chloratum Crystallisatum

Russian: "Hloristyi Kaltzyi Kristallitcheskyi" English: Crystalline Calcium Chloride

$CaCl_2 . 6 H_2O$ Mol. Wt. 219.10

Colorless prismatic crystals, without odor, having a bitter taste, exceedingly hygroscopic, upon being stored in air they melt. The crystals melt in their water of crystallization around 34°C. Soluble in one-quarter part of water bringing about a marked lowering of temperature, easily soluble in alcohol. Its solutions have a neutral reaction.

A solution of calcium chloride (1:20) gives a white flocculent precipitate with silver nitrate which is insoluble in nitric acid, soluble in ammonia solution. Upon addition of a solution of ammonium oxalate to the same solution of calcium chloride (1:20) a white pre-

cipitate is produced which is insoluble in diluted acetic acid, but easily soluble in dilute hydrochloric acid.

Upon addition of one cc. of ammonium chloride solution and ammonia solution having a basic reaction (to litmus) to a (1:20) solution of calcium chloride, no haziness or precipitate should appear either at ordinary (room) temperature or when this mixture is boiled (salts of iron, aluminum and salts of phosphoric acid).

Upon addition to ten cc. of a 1:20 dilution of the salt of five cc. saturated solution of calcium sulfate, the solution should not become hazy (salts of barium). A 1:20 aqueous solution of the salt should not give reactions for salts of sulfuric acid or for salts of heavy metals.

A ten cc. solution of calcium chloride (1:20) is heated to boiling and twenty cc. of a solution of ammonium oxalate are added. After allowing the liquid to stand for three hours it is filtered and the precipitate is washed several times with warm water. The filtrate and washings are evaporated in a beaker on a water bath and the residue is carefully heated to redness, dissolved in a small quantity of distilled water and poured into a porcelain crucible. The beaker is washed with a small quantity of distilled water and these washings are also poured into the crucible. The liquid in the crucible is evaporated on a water bath and the residue is heated to redness. The residue should not weigh more than 0.003 gm. (salts of magnesium, potassium and sodium).

Store in a dry place in not too large glass jars with well-ground glass stoppers or ordinary cork stoppers over which paraffin has been poured.

The reduction in the incidence of toxic reactions from trivalent arsenicals accomplished by ascorbic acid administration is described as due to the lowering of the oxidation potential of the blood. It is believed that arsenical toxicity is increased by in vivo oxidation.

WHAT WE OWE TO GOOD BREEDING

By T. Swann Harding *

DURING wartime turmoil about food we perhaps rarely thought of Gregor Johann Mendel, the Austrian monk and botanist, who discovered the laws of heredity, and then entombed his finding in an obscure Swiss journal from which it was not exhumed until fifty years later. We owe much to him, and to his successors in a long line of plant and animal breeders, and we should have had still less to eat were it not for them.

Things went slowly at first, of course. T. J. Burrill of Illinois discovered that bacteria could spread plant disease in the late 80's, but he did little or nothing to gain acceptance for the discovery. Erwin F. Smith of the Department of Agriculture put it over and firmly established it in a decade of scientific experimentation and active polemics. The discovery was generally accepted by about 1900.

Then William Orton came from New England to enter the picture. He joined the Department of Agriculture to study cotton wilt. He had never seen a cotton plant growing, so he went South to look at one. When he observed his first field of wilted cotton his keen eye detected that some plants were unaffected by the disease. Immediately he wondered if it might be possible to breed cotton plants that would be naturally resistant to destructive fungi and bacteria.

This, as we now know, was possible, and practically every plant and cereal crop you could mention has since been improved by this process. The work goes on continuously and has strange ramifications. Even sheep are streamlined. They are bred to have less hair over their eyes, better fleeces, fewer wrinkles or folds in their skin, and improved meat quality. Differences in beef tenderness are shown to be caused as much by breeding and exercise habits as by the age and feeding of the animals.

Indeed it is rapidly becoming possible deliberately to breed tender beefsteaks on the hoof. Many a tough old steer of the past might have been quite tender had he but had the right breeding. The plant breeder comes nobly along to produce Mohawk, a fancy new potato

* Granite Gables, 400 Linden Lane, Falls Church, Va.

variety especially suitable for baking—combining the already good baking quality of Green Mountain and Katahdin into what can only be called excellence.

We also have inbred chickens in increasing numbers which are vertitable egg machine guns, firing the henfruit more rapidly and regularly than any known in the past. It has just been proved possible to breed strains of hens which lay eggs of better keeping quality! For there are individual and family differences in the keeping quality of eggs, the shells of some being more porous than those of others.

Eggs with porous shells lose weight more rapidly in storage than do those with shells less porous. Hens can be bred whose eggs shrink only about half as much in weight as do those of other hens. So Department of Agriculture scientists, in addition to breeding better steak and potatoes, are also improving eggshell quality through selection of breeding stock, thus producing better-keeping eggs.

Such work is being carried on cooperatively by the Department and every State experiment station in the Nation—one and sometimes two stations to each State, a small State like Connecticut, curiously enough, having two experiment stations. It is an interesting experience to travel around among some of the stations and talk to the plant and animal breeders who are constantly increasing our food supplies and improving their quality.

For instance, Michigan is our leading white-bean-growing State. Its scientists have developed, in Michelite, a new white bean variety which has increased the income of its bean growers by nearly 7 million dollars annually, while decreasing waste from "pick and screenings" by over 1 million dollars a year. This product of research scientists is now so popular that 85 per cent of the State's bean acreage is planted to it.

Here also new potato varieties—Katahdin (named after a mountain in Maine), Chippewa, Pontiac, and New Menominee are estimated to have increased the State's farm income by well over 7½ million dollars a year, though the research involved costs less than five thousand dollars a year. Many of the varieties have been developed jointly by the Department and the States.

Then there are early ripening tomatoes—the orange tree in everyman's backyard. The new Chatham starts to ripen in early August, earlier than any tomato previously available in the Upper Peninsula. Its juice has the nutritive value of orange juice.

There is Great Lakes Head Lettuce, bred not to bolt—throw up a seed stalk as previous varieties had done whenever the temperature went above eighty degrees even for a single day. The Department of Agriculture and the California experiment station had been trying to breed such lettuce with discouraging results. A Michigan State man got hold of some head stocks ready to be discarded. He carried on several more seasons of breeding under Eastern climatic conditions.

Finally a strain was produced which did not bolt. It is becoming a dominant year-round variety now. It now appears as a winter crop in Texas and Florida, a spring crop in Virginia, and a million-dollar-a-year crop in Michigan. The total cost of the research done on it in Michigan has not so far exceeded four thousand dollars.

Up at Iowa State at Ames cooperative work goes on, Federal and State plant breeders being well mixed up together. We have all heard of hybrid corn and of how its development has increased yields 20 per cent. In 1943 the increased yield due to growing hybrid corn was so large, that, turned into pork, as so much of it was, it could have supplied 54 pounds additional for every man, woman, and child in the Nation—some pork barrel indeed.

Oats are further along in breeding than any small-grain crop and stand next to corn. Here the problem has been to breed strains resistant to crown rust, stem rust, and the smuts which afflict oats and all but destroyed the crop in what used to be "poor" oat years. So successful has this work been that the former "poor" years, the moist ones during which oat diseases raged, have now become the "good" years.

Oat strains imported from Australia and the Argentine were combined with various American strains and ultimately varieties were developed which resisted both the rusts and the smuts. Yields increased approximately 9 bushels per acre for the entire State of Iowa. There was an average increase of 32 per cent in yields under experimental conditions.

More important, during 7-year trials making direct comparisons between susceptible and resistant varieties grown under identical conditions, yields were greater for the former by over 19 per cent right in farmer's plots. During the 7 years Iowa oat growers received from 25 to 50 million dollars more for their crop than they would have, had they not had resistant strains.

The acreage of disease-resistant oats spreads constantly. All Iowa acreage will be planted to such strains this year, but other States are following suit. Wisconsin has already gained sufficient from resistant oat strains in 1 year to pay for all its State experiment station work during the past 20 years. Dividends are high. Indeed such dividends, paid in the form of improved farmer income, so overcompensate for the expense of research that the Department of Agriculture, the State experiment stations, and the land-grant colleges really cost taxpayers nothing whatever.

Up in New Haven the other day D. F. Jones, who is a wizard at breeding hybrid corn adapted to local needs, was discovered fooling with chestnuts. As you know the blight has practically wiped out the American chestnut, which was an excellent producer of lumber as well as of nuts.

Jones has been importing blight-resistant chestnut strains which, however, do not have the erect habit of growth of the American chestnut nor its ability to produce lumber. But they do yield nuts early and plentifully. By crossing them with suckers which still come from the roots of blight-killed American chestnuts, a better variety is being developed. When ready it will be an excellent producer of nuts and lumber, will have the American habit of growth and be resistant to blight.

In short, the plant or animal breeder of today simply sets down the qualities he would like his ideal plant or animal to have, then blends them and breeds accordingly. He can breed both for resistance to disease or for improved quality as food. For instance, evidence has been developed that chickens can be bred free of lymphomatosis or fowl paralysis.

This disease mysteriously entered the United States from Europe around 1917. It spread rapidly. Soon one-fourth of the chickens in New England had it. We have never been able to rid our flocks of it and the disease costs American poultry growers $50,000,000 a year and, of course, deprives us of many chickens we should otherwise have available for food.

Fortunately some years ago Henry A. Wallace decided that long-time research should be undertaken to build up reservoirs of good germ plasm, plant and animal. Henry knew about that. He was one of the pioneers, one of the two or three top men, in bridging the gap between pure research and practical use in the field of hybrid corn.

He also knew the profits in good plant germ plasm, for his shrewd financial insight enabled him to build up a sound and very profitable business in hybrid corn.

Anyway Congress took heed of him and, as a result, the Bankhead-Jones Act of 1935 was passed (the Jones here is the former War Food Administrator) which provided funds for long-distance research leading to nothing of immediate practical value but destined, as always, to bring big profits in the end. As a result the Department of Agriculture established nine Bankhead-Jones Laboratories in different places.

Some of these were centralized, some highly decentralized. Each was assigned a difficult problem which it was known would require long-time research to turn up anything of value. Each closely cooperates with the land-grant colleges and experiment stations of several States. Some are so decentralized that practically all their equipment and staff is derived from the States.

At East Lansing, Michigan, the Regional Poultry Research Laboratory is highly centralized under its Director, Berley Winton. While Michigan State donated the land upon which it stands, it has a fine little laboratory building, complete equipment for poultry raising, and a Federal staff of about thirty. It is attacking the problem of chicken paralysis pathologically, nutritionally, cytologically (studying tissue cell structure) and by the good old genetic method of Gregor Mendel.

Since nobody knows how fowl paralysis spreads, the utmost precautions must be taken. One chicken caretaker changes his clothes 64 times a day and has a different suit and shoes for entering each pen of chickens to gather eggs and to clean and feed the poultry. Every nonhatching egg and every dead chicken is examined with great care by the pathologists and cytologists.

Inbreeding has been used as with corn and hogs. Already lines that are from 25 to 59 per cent pure have been bred. These can be combined and various defects eliminated. Many lethal characters, some quite new, have been uncovered and are being eliminated in this inbreeding. It appears that the disease can be transmitted through the eggs—an important finding.

Furthermore lines of chickens that are quite resistant to fowl paralysis have already been bred and resistance can probably be built up still further. Susceptible lines have been bred but, unfortunately,

they lay so poorly it is difficult to keep them in existence, though they can be maintained free from fowl paralysis. So the work goes on from these interesting leads and is certainly destined in time to be of the utmost value both scientifically and financially.

Quite as interesting is the Bankhead-Jones Regional Swine Laboratory at Ames, Iowa, directed by Wm. A. Craft. It is highly decentralized, depending on the States for equipment, facilities, and most of the staff. Here the main idea is to do with hogs what has already been so successfully done with corn, only you get inbred hogs and hybrid corn. While hogs are being raised on cement with almost machine-like precision by many expert growers, it is a fact that we have much yet to learn about feeding and breeding these animals.

So the investigators at this laboratory set up certain objectives. They would like hogs to be more prolific and to have more vigor when first born; they would like to promote suckling ability, large hams, better bacon quality, smoothness of coat, economy in the use of feed; they would like to produce lardiness or freedom from excess fat at will. They would, finally, like to eliminate certain defects like blindness, ear deformities, swirls in the coats, and so on.

Again resort is had to the good Austrian monk's fundamental principles. Stock from different areas, often differing markedly in type, conformation, and color, is crossed. The crossbred stock are then inbred. Selection is made from the inbreds to meet needs. In short, the genes are put into a hopper and mixed in the desired proportion, and the speed of breeding for desired qualities has already been stepped up tenfold.

The long-time objective is to discover, develop, and test both breeding and selection procedures. This will still further speed hog improvement, at least from our standpoint and that of the growers, whatever the hogs may think about it in moments of melancholy reflection. Generally speaking the effort is to use inbred lines of swine as inbred lines of corn have been used by the plant breeders.

Approximately 42,000 pigs have already been produced on this project. Some 42 inbred lines have been produced and retained, and this throws purebreeding into high gear. On the whole the results resemble those with hybrid corn.

Already lines have been bred which produce 3 per cent more lean meat and there has been a 5 per cent gain in over-all efficiency by inbreeding. The inbred lines produce more pounds of meat per pound

of food eaten. There has been a large gain in survival after birth, in vigor and in the rate of growth.

For the present the investigators are aiming to increase the number of pigs farrowed, the weight and number of pigs weaned, and the rate of growth from weaning to the attainment of market weight 5 or 6 months later, and to improve the general desirability of the pigs produced, at market weight. Progress is being made, though the practical economic value of the procedures developed remains to be determined.

However, neither practice nor profit can be kept too closely in mind when one is engaged in such work. Gregor Mendel was not trying to improve yields or make money when he did his fundamental work on the laws of genetics. He was playing around with sweet peas for his own edification and diversion. He salted his results away where they remained secret a half century.

On the other hand the agricultural investigators who sought to combat hog cholera were trying to solve a really practical problem, but were not sure they could do so. Yet their researches, costing about $50,000, now save hog growers at least 12 million dollars *every year*. The investigators who developed methods of protecting man against trichinosis ran up an expense account of $30,000, but they save us at least 5 million dollars *each and every year*.

Trace these things back through, and you come invariably to the fellow whose stimulus was pure intellectual curiosity and who performed research just to find out hows and whys and wherefores. It never occurred to him that six research projects carried on in one State at a cost of only $76,000 would increase that single State's farm income by $16,370,000 annually. The State is Michigan, and the work was done at its agricultural experiment station.

But those pioneers had their pleasure and their intellectual diversion. Others turn pure research into practice and reap the profits. All research pays huge dividends, 500 to 10,000 per cent—and the banker who promised you that you would dismiss as a fraud.

What of the future? Undoubtedly plant and animal breeding will be used more and more to improve the nutritive quality of food. After destructive diseases and insects have been controlled and resistant lines bred, the next thing will be to produce lines with enhanced vitamin and mineral content, perhaps even with improved proteins or

increased fats or carbohydrates. Relationships between the soil and growing plants and animals also will be studied more closely.

Some progress has already been made in breeding sweet potatoes with a higher carotene content and cabbage and snap beans containing greater quantities of ascorbic acid or vitamin C than usual. Substantial progress has also been made in breeding plants for quality, flavor, canning purposes, sugar content, freezing, or dehydration. The thiamin content of wheat can doubtless be improved, which would be far better than "enriching" the flour afterwards.

Many varieties of plants and fruits differ naturally from one another in vitamin and in mineral content. Meat animals can be induced, as we saw above, to grow tenderer steaks, more lean meat, or more fat, as desired. Plant breeders can undoubtedly produce strains of plants which are especially efficient in extracting calcium, phosphorus, iron, or other minerals from the soil. In short, not only greater yields but more nutritive food products will be sought. The sky is the limit. Leave it to the breeders to try to touch the sky.

Penicillin by Inhalation. N. Mutch and R. E. Rewell. *Lancet* 1:650, May 26, 1945; through *U. S. Naval Med. Bull. 45,* 620 (1945). When calcium penicillin was administered as a mist, it was found to be rapidly absorbed through the respiratory mucous membrane, and the titer of the drug in the blood was comparable to that obtainable by the intramuscular and intravenous routes.

Although the wastage of the drug was from 60 to 75 per cent, the high levels of the drug found in the blood and urine suggest that perhaps solutions less concentrated than 5,000 units per cc. can be used successfully and economically in the local treatment of such conditions as purulent bronchitis and bronchiectasis, and as a prophylactic against secondary pyococcal infections in influenza.

SELECTED ABSTRACTS

"Ten-Eighty," a War-Produced Rodenticide. E. R. Kalmbach. *Science 102,* 232 (1945). Tests carried out on more than a thousand substances, largely synthetic, indicated that sodium fluoroacetate, referred to under its laboratory serial number, "1080," holds considerable promise as a practical rodenticide.

Preliminary trials were conducted with albino rats; in later tests captive wild Norway rats, prairie dogs and other field rodents served as experimental animals. The more promising substances were finally tried under actual field conditions. Compound "1080" was found to be extremely toxic to a variety of small mammals, but may also constitute a hazard to human beings, domestic livestock and pets, and beneficial wildlife. Among the approximately LD 50 per cent doses for "1080" which were determined are the following: wild black rats, 0.1 mg./Kg.; wild Norway rats, 5.0 mg./Kg.; meadow mice, 0.5 mg./Kg.; black-tailed prairie dogs, 2.5 mg./Kg.; domestic dogs, 0.35 mg./Kg.; and Leghorn hens, 10.00 mg./Kg.

Since "1080" possesses high toxicity to small mammals, very dilute aqueous solutions of it reduce to a minimum any objectionable taste which might lessen its acceptance by rodents. Trials of aqueous solutions of "1080" in rat control in the Southern States yielded results seldom if ever equalled by any other poison.

Studies are being continued by various Federal, State and local agencies and the Armed Services both here and abroad to determine fully the action of "1080" before it is adopted for widespread use.

The γ-Isomer of Hexachlorocyclohexane (Gammexane). R. E. Slade. *Chem. and Ind.* No. 40, 314 (1945). The author traces the history of 1,2,3,4,5,6-hexachlorocyclohexane (also called benzene hexachloride, $C_6H_6Cl_6$ or "666") since it was first prepared by Michael Faraday in 1825 to the present time.

In 1942-3 samples of "666," prepared by chlorinating benzene in the presence of light, followed by recrystallization from benzene,

were tried as an insecticide, particularly as a replacement for derris. The use of several hundreds of tons of a powder containing "666" revealed that it was at least as effective against the turnip flea beetle as powders containing derris, and had no deleterious action on plants.

Inasmuch as results were sometimes inconsistent, efforts were made to separate the product into its several isomers, four of which were known to exist. It was demonstrated that the α (m. p. 157.5-158°) and β (m. p. 309°) isomers are relatively inactive toward weevils; in contrast, the γ isomer (m. p. 112.5°) was found to be more toxic than any other substance ever tested by the author. It was established that the active principle of crude "666" is γ-1,2,3,4,5,6-hexachlorocyclohexane (Gammexane), present to the extent of 10-12 per cent.

The δ isomer (m. p. 138-139°) is also known. The pure isomers are separated by fractional crystallization from methanol and from chloroform. The structure of the β isomer is definitely known from X-ray analysis, but the other isomers have not been subjected to such examination. Several photographs of atomic models are presented to show the probable configuration of the four isomers.

The chemical and physical properties of the four isomers, including a comprehensive tabulation of their respective solubilities in various organic solvents, are enumerated, and toxicity studies on rats and gold fish are reported.

Several methods of using Gammexane as an insecticide were investigated. As a dusting powder, 20 per cent of crude "666" was mixed with 80 per cent gypsum, which preparation was further diluted with selected materials. When solutions were desired, xylene, carbon tetrachloride, perchloroethylene or decahydronaphthalene were used as solvents. Through the use of Turkey red oil, stable emulsions may be prepared.

A form of Gammexane readily dispersible in water may be prepared from crude "666" by incorporating an adequate amount of the waste lye resulting from the sulfite treatment of cellulose.

Data are presented in tabular form on the insects and certain other pests found to be killed by Gammexane, and on the relative toxicity of the "666" isomers, D. D. T., and cuprous cyanide toward several insects.

It is suggested that the mode of action of Gammexane may be due to its similarity in structure to inositol, which is a metabolite of widespread occurrence in many types of cells. It is possible that Gammexane is absorbed from the outer surface of the insect and is then distributed throughout some portion of the organism to the cells where a vital reaction is blocked, resulting in the death of the organism.

Curare in the Acute Stage of Poliomyelitis: Preliminary Report. N. S. Ransohoff. *J. A. M. A. 129,* 129 (1945). The treatment of four consecutive cases of acute anterior poliomyelitis by the administration of a curare preparation ("Intocostrin" Squibb) in doses of 0.9 mg. per Kg. was followed by dramatic improvement in the symptoms exhibited. Brief reports on these cases are presented.

Prompt relief of nuchal rigidity, muscle spasm, opisthotonos and pain was observed in the patients, who ranged in age from two and one-half to thirteen years. In only one of the four cases mentioned in this preliminary report was it necessary to administer a second dose of the drug.

It is not known whether the dosage of 0.9 mg. per Kg. is the ideal amount, but the author feels that in the more severe cases and in older children it will probably be necessary to increase this dose.

Penicillin in Iodized Oil for Instillation Into the Lungs. M. J. Romansky, D. J. Dugan and G. E. Rittman. *Science 102,* 255 (1945). A suspension of calcium penicillin in 40 per cent iodized oil, in a concentration of 1,500 units per cc. of finished preparation, was prepared in a sterile mechanical blendor. In preliminary experiments on anesthetized rabbits 1 to 3 cc. doses of the preparation were injected through the trachea into the bronchi, and the presence of the penicillin iodized oil in the tracheobronchial tree demonstrated by X-rays. Blood levels of from 0.039 to 1.25 units per cc. were found at fifteen minutes, thirty minutes, one and two hours, depending upon the amount of the preparation instilled. Gross and micro-

scopic studies of the lungs and other organs of the animals, performed after two months of observation, failed to reveal any abnormalities.

Ten human patients with saccular bronchiectasis and two with pulmonary abscess received 7 to 10 cc. each of the penicillin iodized oil by the supra-glottic inhalation method, after preliminary cocainization of the posterior pharynx. No discomfort resulted from this treatment. Only occasionally were assayable levels of penicillin found in blood samples withdrawn at fifteen minutes, thirty minutes, one, two and three hours after the single instillation of the preparation. Urinary excretion of penicillin, however, was observed in all patients for at least twenty-four hours.

No significant clinical results were noted; in two cases there was a gradual reduction in sputum to about 50 per cent of the original amount by the seventh day, returning to the previous status by the end of two weeks.

The authors suggest the possibility that the treatment described may alter the bacterial flora of the diseased lungs and make subsequent surgical procedures safer.

Stability tests on the penicillin iodized oil indicated that it did not deteriorate when stored for sixty days in the refrigerator, at room temperature or at 37°C.

Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1944, with Special Reference to Arsenical Dermatitis. O. L. Burton, G. W. Justyn and L. T. Anderson. *U. S. Naval Med. Bull. 45,* 783 (1945). During 1944 medical officers of the U. S. Navy administered a total of 396,144 doses of arsenicals and noted the occurrence of a total of eighty reactions. Mapharsen was given in the majority of cases; 381,475 doses produced thirty-eight mild reactions, twenty-four severe, and five fatal. Much less frequently administered was neoarsphenamine, 12,398 doses of which resulted in four mild reactions, six severe and three fatal.

No reactions were noted following the administration of 2,027 doses of tryparsamide, 190 doses of bismarsen and fifty-four doses of sulfarsphenamine.

Dermatitis in some form was observed in twenty-six of the total of eighty reactions, which are subdivided as follows: mapharsen, eight mild and eleven severe; neoarsphenamine, two mild and five severe. Case reports are given for all twenty-six patients who developed arsenical dermatitis.

Tabular data summarize for the twenty-year period 1925-44 the number of doses of arsenicals administered, the severity of reaction noted, and the ratio of doses to reactions. In addition to the drugs previously enumerated, the following arsenicals, which were not administered in the U. S. Navy in 1944, are included: acetarsone, arsphenamine and silver arsphenamine.

The Administration of Penicillin: A Simplified Technic. N. W. Clein. *Northwest Med. 44,* 309 (1945). Based upon clinical observations in approximately one hundred cases, the author suggests a simplified technic for the intramuscular administration of penicillin. Instead of employing the customary 20 cc. of normal saline solution or distilled water to dissolve 100,000 units of penicillin, he uses 5 cc.; thus, a 1 cc. injection represents 20,000 units of the drug. Patients who received 1 cc. injections remarked favorably on the absence of pain, burning or soreness at the site of injection.

In this procedure the patient receives four injections, instead of the usual eight, in a twenty-four hour period. This has the advantage of being less disturbing to the patient, and is claimed to avoid the necessity of awakening him from sleep in order to administer medication. In addition, this method conserves the time of the hospital personnel.

As the condition of the patient improves, both the number and amount of injections are reduced. A report on a case of infection of the upper respiratory tract is presented to illustrate the suggested technic. This patient received a total of 14.5 cc. of penicillin solution, containing 290,000 units, administered in sixteen injections over a five-day period.

The therapeutic results achieved by the proposed technic are stated to be equal to or better than those obtainable through the use of the standard method.

SOLID EXTRACTS

A National Memorial for Nurses of World War II has been proposed to be located in Washington, D. C. A campaign to raise at least $2,000,000 for the project has been started with Mrs. Norman T. Kirk, wife of the Surgeon General of the Army, and Mrs. Ross T. McIntire, wife of the Surgeon General of the Navy, serving as co-chairmen under Arthur H. Johnson of Washington. The memorial is to take the form of a social center and temporary residence open to all medical women of the Army, Navy and Air Corps.

AJP

T. W. Delahanty, writing in the Foreign Commerce Weekly, *gives a very optimistic outlook for our Foreign Market in the field of drugs and pharmaceuticals. A $100,000,000 annual volume is considered likely. This is equivalent to the prewar volume consumed by twenty-seven states in this country with one-third our total population. Mr. Delahanty believes that more small firms should share in this market and his full article should be of interest to all export managers.*

AJP

The claim that massive doses of vitamin C are useful in treating hay fever and other allergies is now disputed. Saturation blood levels of ascorbic acid failed to produce any change in the course of hay fever or asthma according to a paper recently published.

AJP

A study of the time spent per patient by the average general practitioner and reported in Public Health Reports *reveals that the average time spent per patient was 16.9 minutes, with a variation among physicians from 12.2 to 21.3 minutes. As a further evidence that physicians are but human it was reported that "the average time per patient decreased steadily as the number of patients per office period increased."*

The Eriez Manufacturing Company of Erie, Pa., has developed a powerful compact non-electric magnetic separator for the removal of large and microscopic iron and steel particles from the raw materials used in the manufacture of cosmetics, perfumes, pharmaceuticals, etc. The savings to expensive equipment fully justify such installations.

AJP

A recent article in the Journal of the A. M. A. recommends discontinuing Boric Acid from general use as an antiseptic. The author, Dr. E. H. Watson, contends that "when a drug can be shown to be almost entirely ineffective and at the same time dangerous even when used in ordinary ways it is time to remove that drug from general use as rapidly as possible." Dr. Watson cited the fatal poisonings on record where it has been erroneously incorporated in baby food and other evidences of toxicity and pointed out that there are many superior antiseptics which are far safer.

AJP

A study has shown that 82 per cent of the women graduates in medicine remain in full-time medical work, matrimony notwithstanding. This figure is cited as complete justification for the training of women physicians. A similar study of women pharmacists conducted by Dr. Tom Rowe in behalf of the American Association of Colleges of Pharmacy should, when the results are released, prove quite interesting.

AJP

Hydrogen Peroxide 90 per cent plus by weight is now commercially available from the Buffalo Electrico-Chemical Co. It is stable and not hazardous to handle. One gallon yields over 400 gallons of oxygen gas and it has many important applications due to its powerful oxidizing actions. Quantities are now available with the discontinuance of rocket warfare.

NEW LAMINATED PELLET

FOR

PROPHYLAXIS AND THERAPY OF MULTIPLE VITAMIN DEFICIENCY

EACH PELLET CONTAINS

8 VITAMINS

Vitamin A From fish liver oil	5000 U.S.P. units
Vitamin B_1 Thiamine Hydrochloride	2 mg.
Vitamin B_2 Riboflavin	2 mg.
Vitamin B_6 Pyridoxine Hydrochloride	0.5 mg.
Calcium Pantothenate	1 mg.
Niacinamide	20 mg.
Vitamin C Ascorbic Acid	50 mg.
Vitamin D Chemically pure synthetic vitamin D_2 (calciferol) from ergosterol	1000 U.S.P. units

PLURAVIT...

Trademark Reg. U. S. Pat. Off.

Brand of MULTIPLE VITAMINS

• • SMALL, EASY TO SWALLOW, PLEASANT TASTING PELLETS, WITHOUT AFTER-TASTE.

This Winthrop product is being intensively promoted to physicians. Boost your sales of Pluravit by maintaining adequate stocks. Place your order today with your wholesaler.

WINTHROP CHEMICAL COMPANY, INC.
PHARMACEUTICALS OF MERIT FOR THE PHYSICIAN
NEW YORK 13, N. Y. WINDSOR, ONT.

double control

Pathogenic Bacteria

Tyrothricin, the new, stable antibiotic for topical use, has proved remarkably effective against certain organisms (streptococci, staphylococci, pneumococci, diphtheria bacilli) commonly encountered in upper respiratory tract infections.

Nasal Congestion

'Propadrine' Phenylpropanolamine Hydrochloride is a local vasoconstrictor and bronchodilator with ephedrine-like properties. It is notably free of untoward side-effects such as excitation, sleeplessness and restlessness commonly encountered with drugs of this nature.

'PROTHRICIN'

Antibiotic Nasal Decongestant containing Tyrothricin and 'Propadrine' Hydrochloride

'PROTHRICIN' combines the *antibiotic activity* of Tyrothricin and the *vasoconstricting action* of 'Propadrine' Hydrochloride to provide a double control for the symptomatic treatment of nasal congestion accompanying bacterial infections.

'PROTHRICIN' is an ideal topical nasal application because:

It is an isotonic buffered solution with a *pH of 5.5 to 6.5*—same pH as nasal secretions.

It maintains *antibiotic action in the presence of pus and mucosa.*

It is relatively *nonirritating* and *nontoxic* to nasal and sinus mucosa.

Its *low surface tension* (approximately 40 dynes per centimeter) affords sufficient penetration into the interstices of the mucosa to combat acute infection.

It *does not interfere* with the normal defense mechanisms of the mucosa.

It *does not form a crust* that interferes with drainage.

It *does not abolish* ciliary activity.

'PROTHRICIN' is indicated in the relief of nasal congestion accompanying the common cold, allergic rhinitis, acute catarrhal rhinitis, acute rhinosinusitis and acute ethmoiditis.

Applied by means of tampons, irrigation, drops or spray. Supplied in 1-ounce bottles with dropper assembly. Sharp & Dohme, Phila. 1, Pa.

The active ingredients of this preparation are:

Tyrothricin (antibiotic) . . . . 0.02% (200 micrograms per cc.)

'Propadrine' Hydrochloride . . 1.50% (vasoconstrictor)

Sharp & Dohme

All in favor raise right hands . . . *with wallets*

Naturally we want our boys home.

But how much are we willing to do about it?

Are we willing to pay for bringing them back? If we are, we'll buy *extra* Bonds in the Victory Loan.

And after these fellows get home—what then?

We want to take care of the injured ones, of course. We want to give our boys a chance to finish their education. We want to see that there are plenty of decent jobs for them.

How much are we willing to do about that?

If we're really serious about wanting to see that our men get what they have so richly earned, we'll buy *extra* Bonds in the Victory Loan.

Now's the time. Let's have a show of hands—with wallets—to prove how much we really want to hear that familiar voice yelling "It's *me!*" Let's prove, with pocketbooks, that we can do our job as well as they did theirs.

THEY FINISHED THEIR JOB—

LET'S FINISH OURS!

VICTORY LOAN

AMERICAN JOURNAL OF PHARMACY

This is an official U. S. Treasury advertisement—prepared under auspices of Treasury Department and War Advertising Council